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## Delirium assessment in neuro-critically ill patients: A validation study

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## **Delirium assessment in neuro-critically ill patients**

### **A validation study**

Krone Larsen, Laura; Frøkjær, Vibe G.; Stub Nielsen, Jette; Skrobik, Yoanna; Winkler, Yvonne; Møller, Kirsten; Christin Petersen, Marian; Egerod, Ingrid Eugenie

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**Word Count:****Conflicts of interest**

The authors have no conflicts of interest to declare.

**Abstract**

**Background:** Delirium is under-investigated in the neuro-critically ill, although the harmful effect of delirium is well established in patients in medical and surgical intensive care units (ICU) . To detect delirium, a valid tool is needed. We hypothesized that delirium screening would be feasible in patients with acute brain injury and we aimed to validate and compare the Confusion Assessment Method for the ICU and the Intensive Care Delirium Screening Checklist against clinical International Classification of Diseases-10 criteria as reference.

**Methods:** Nurses assessed delirium using the Confusion Assessment Method for the ICU and Intensive Care Delirium Screening Checklist in adult patients with acute brain injury admitted to the Neurointensive care unit (Neuro-ICU), Copenhagen University Hospital, if their Richmond agitation-sedation scale score was minus 2 or above. As the reference, a team of psychiatrist assessed patients using the International Classification of Diseases-10 criteria.

**Results:** We enrolled 74 patients, of whom 25 (34%) were deemed unable to assess by the psychiatrists, leaving 49 (66%) for final analysis. Sensitivity and specificity for the Confusion Assessment Method for the ICU was 59% (95% CI 41-75) and 56% (95% CI 32-78), respectively and 85% (95% CI 70-94) and 75% (95% CI 51-92), respectively for the Intensive Care Delirium Screening Checklist.

**Conclusions:** Our findings suggest that the Intensive Care Delirium Screening Checklist may be a valid tool and the Confusion Assessment Method for the ICU is less suitable for delirium detection for patients in the Neuro-ICU. In the neuro-critically ill, delirium screening is challenged by limited feasibility.

*Clinicaltrials.gov identifier no. NCT02594982*

**Keywords:** Delirium, acute brain injury, neurointensive care unit, Intensive Care Delirium Screening Checklist (ICDSC), Confusion Assessment Method for the ICU (CAM-ICU), International Classification of Diseases -10 (ICD-10).

## Editorial Comment

Delirium is common among ICU patients and it is associated with unfavorable outcomes. To further explore the pathophysiology behind delirium and to evaluate possible treatments, objective and standardized means for diagnosis of delirium are needed. This study assessed several simplified rating systems for diagnostic accuracy compared to psychiatrist performing an ICD-10 diagnosis of delirium in patients in a neurointensive care setting.

## Introduction

Delirium detection using a valid screening tool, such as the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC), substitutes clinical evaluation using diagnostic criteria in many ICU studies<sup>1-4</sup>. This pragmatic approach is limited by confounders, such as sedation-related level of consciousness<sup>5</sup>, and may not apply to the neuro-critically ill. Invoked barriers to screening patients in the neuro-ICU include considering delirium as brain dysfunction on the encephalopathy continuum, and coma, aphasia, deafness, or other neurologic communication barriers<sup>6</sup>.

Two commonly used instruments<sup>7</sup>, the Confusion Assessment Method for the ICU (CAM-ICU)<sup>8</sup> and the Intensive Care Delirium Screening Checklist (ICDSC)<sup>9</sup> both assign one of the following three ratings to patients: positive, negative, or unable to assess (UTA). In addition, the ICDSC also differentiates between no delirium, subsyndromal delirium, and delirium<sup>10</sup>. The original ICDSC validation study was performed on a mixed ICU population and included neurologically critically ill<sup>9</sup>. A subsequent multicentre feasibility and reliability study in adult patients in three Neuro-ICU's showed feasibility and good concordance in 75% of all evaluations<sup>11</sup>. By contrast, the original CAM-ICU validation study did not include patients with a neuro-critically diagnosis<sup>8</sup>. A later study limited to patients with stroke reported that delirium as detected by the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria was present in 42,6%; the CAM-ICU had a sensitivity of 76% and a specificity of 98% compared to DSM-IV<sup>12</sup>. Included patients had a nearly normal level of consciousness based on their median admission Glasgow Coma Scale (GCS), 14.5<sup>12</sup>. In a recently published letter, the CAM-ICU and the ICDSC were

compared in patients with mild and moderate traumatic brain injury (TBI), a median admission GCS of 14, and a mean APACHE II score of 11.5 (+/- 6.4). The sensitivity and specificity was 62% and 74% with the CAM-ICU and 64% and 79% with the ICDSC<sup>13</sup>. Thus, the current knowledge of delirium in neuro-critically ill patients appears to be related to patients with relatively mild brain dysfunction and with mild to moderate illness severity.

The importance of delirium assessments in the ICU<sup>14</sup> derive from its association with poor outcomes such as length of stay, mortality, and cognitive impairment<sup>15-19</sup>. This has led to a broad endorsement of the CAM-ICU and the ICDSC in critical care settings. Expert European Society of Intensive Care Medicine panellists and the most recent Pain, Agitation and Delirium (PAD) Society of Critical Care Medicine guidelines strongly recommend the use of delirium screening using the two instruments<sup>3,20</sup>. Yet, no study has validated delirium screening in a mixed Neuro-ICU population. Rigorous delirium screening tool validation and comparisons, that consider feasibility and cofounders as level of consciousness, are necessary in this vulnerable population to ensure scientifically grounded 'diagnosis- equivalents' before considering prevention, treatment and outcome studies. Accordingly, we prospectively evaluated patients with acute brain injury; traumatic and non-traumatic injuries, using the International Classification of Diseases (ICD)-10 as reference. We hypothesized that the neuro-critically ill are assessable for delirium and we aimed to evaluate and compare the validity of the CAM-ICU and the ICDSC for delirium assessment in patients with acute brain injury using the ICD-10 criteria as reference.

## **METHODS**

### **Site and Setting**

This prospective single-centre study was conducted at Copenhagen University Hospital, a 1300 bed tertiary referral hospital covering a catchment area of 2.6 million citizens in eastern Denmark.

### **Participants**

From August 15<sup>th</sup>, 2015 to June 30<sup>th</sup>, 2016 all admitted adult patients in the Neuro-ICU with acute brain injury from TBI or ischemic or haemorrhagic stroke with an anticipated stay of 48 hours or more were included. We excluded patients with pre-existing severe brain injury, children, and patients whose therapeutic aim was palliative care.

### **Sample size**

Based on a sensitivity of 90% an assumed delirium prevalence of 50% and a 95% confidence interval (CI) within +/- 10%, the sample size required to validate the scales was a minimum of 70 patients.

## **Data collection**

### *Psychiatric assessment*

A team consisting of one consultant psychiatrist and three physicians undergoing advanced specialist training in clinical psychiatry (hereafter termed psychiatrists) conducted the delirium assessment using ICD-10 criteria on the day that the patient first became assessable, defined as a best Richmond agitation-sedation scale (RASS)<sup>21</sup> score of minus 2 or above. The psychiatrist retrieved information from the primary nurse, physician, and hospital chart for the previous 24 hours and diagnosed the patient as either ICD-10 delirium-positive, delirium-negative, or unable to assess (UTA). The psychiatrists' assessments were performed independently and kept in sealed envelopes throughout the study, and were unavailable to the ICU staff as well as the primary investigator (first author, LKL). During the study period, the three psychiatrists performed four supervised co-ratings with the consultant psychiatrist and eight pairwise mutually blinded ratings with perfect inter-observer agreement.

### *Nurse assessment*

The ICDSC was translated from English to Danish by three of the authors (LK Larsen, M Petersen and I Egerod) in collaboration with, and approved by, the instrument's developer (Y. Skrobik). The instrument was translated and back-translated in accordance with formal methodology<sup>22</sup> according to the Swedish translation study on ICDSC<sup>23</sup>. An existing validated Danish version of the CAM-ICU was already in use<sup>24</sup>. First author and a team of clinical ICU nurses, specially trained in the use of both ICDSC and CAM-ICU for this project, assessed the patients two or three times daily (day/evening/night) depending on the shift duration (8 or 12-hour shifts).

The ICDSC worksheet was completed by first author and the nursing team at the end of each shift. First author performed most of the daytime assessments in collaboration with the ICU nurse caring for the patient, and the team of clinical nurses performed assessments during evening and night shifts. The CAM-ICU worksheet (available on [www.icudelirium.org](http://www.icudelirium.org)) guides the assessment in the following order:

- acute change or fluctuating course of mental status)

- inattention (Picture test or letter test using the letters SAVEAHAART)
- altered LOC (current RASS)
- disorganized thinking.

As inattention is a ‘sine qua non’ criterion for a CAM-ICU delirium-positive score, the patient was considered CAM-ICU negative if the inattention test was passed, and no further assessment was made. The patient was recorded as ICDSC/CAM-ICU delirium-positive if there was at least one positive assessment that day. If all assessments were negative, the patient was recorded as ICDSC/CAM-ICU delirium-negative for that day. We performed inter-rater reliability (IRR) testing between first author and the team of clinical nurses. The paired ratings required that two raters were present at the same time in the ICU; these were therefore carried out throughout the 11-month study period, minimizing time confounding<sup>25</sup>. All paired raters were blinded to each other’s results.

### **Outcome measures and statistical analysis**

Performance test characteristics for CAM-ICU and ICDSC were calculated using a two-by-two frequency table with standard equations for sensitivity, specificity, positive and negative predictive value, and overall accuracy. For the ICDSC, a scale ranging from 0-8, the area under the receiver operating characteristic curve (AUROC) was used to identify the optimal cut-off score for this population. Categorical variables were compared between patients that were judged as assessable and UTA using Chi-squared, Fisher Exact test (as appropriate). The Mann-Whitney *U* test was used for comparison of continuous variables. All statistical tests were two-sided and statistical significance was set at 0.05. We used kappa ( $\kappa$ ) statistics for IRR testing of the CAM-ICU and the overall agreement of ICDSC was calculated by the Interclass Correlation Coefficient (ICC). Analysis was performed using IBM SPSS, version 22.

### **Ethics**

The study was approved by the National Committee on Health Research Ethics (file number H-15007689) and the Danish Data Protection Agency, and was registered in an international trials database (*ClinicalTrials.gov* identifier no. NCT02594982). In accordance with Danish law, the patient’s next of kin and general practitioner surrogate consent was provided in patients with temporarily impaired decision-making capacity.

### **RESULTS**



### *Study population*

We enrolled 74 patients for this study, but only 49 patients were included in the final analysis. Collected data included gender, age, diagnosis, severity of disease Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II, level of consciousness at admission and during assessment using GCS, sedation and agitation level using RASS, type of sedation, and mechanical ventilation status.

**[Fig. 1 Patient flow diagram]**

### *Prevalence of delirium according to ICD-10*

The seventy-four patients enrolled in the study (Figure 1) were seen by a psychiatrist, on average, within a three hour range from the CAM-ICU and ICDSC nurse evaluation. Twenty-five of the seventy-four patients (34%) were reported as UTA by the psychiatrists. Reasons given by psychiatrists for evaluating as UTA were low level of arousal at time of assessment ( $N=15$ ), inability to communicate (verbally or non-verbally) ( $N=9$ ), or insufficient information in the hospital chart ( $N=1$ ). Patients assessed as by psychiatrist as UTA were not included in the final analysis. Of the remaining 49 assessable patients, 33 (67%) patients were assessed as ICD-10 delirium-positive.

### *Patient characteristics (Table 1)*

There was no difference in gender ( $p=0.37$ ), age ( $p=0.09$ ), APACHE II ( $p=0.65$ ) or SAPS II ( $p=0.07$ ) between patients who were assessable and UTA. However, patients UTA had a lower GCS at admission ( $p<0.05$ ) and during delirium assessment ( $p<0.001$ ) than assessable patients. Also, the assessability of patients varied according to diagnosis ( $p<0.05$ ), with fewer patients with SAH and more patients with TBI in the UTA group. During their stay in the Neuro-ICU, 52 of the 74 patients (70%) received mechanical ventilation and continuous sedation. Compared with assessable patients, more patients UTA were intubated and sedated during their ICU stay (61% vs 88%,  $p<0.05$ ) and ventilated at the time of assessment (10% vs. 36%,  $p<0.05$ ).

**[Table 1 Patient characteristics ( $N=74$ )]**

### *Validity of CAM-ICU and ICDSC vs. ICD-10*

The ICDSC had an AUROC of 0.77 (Figure 2). As in the original validation study [7] a cut-off score of 4 yielded the best sensitivity and specificity (Appendix 1). A two-by-two frequency table comparing the ICD-10 and CAM-ICU or ICDSC, respectively (Table 2) shows twelve false-negative and seven false-positive CAM-ICU assessments. For all twelve false-negative assessments, patients passed the inattention test with 0-1 errors (Letter or picture test). Patients were considered CAM-ICU delirium-negative if they weren't inattentive, according to the CAM-ICU training manual<sup>24</sup>. One patient with a false-positive CAM-ICU assessment was<sup>26</sup> subsequently noted to suffer from expressive aphasia. ICDSC generated five false-negative and four false-positive assessments (Table 2). In two of the five false-negative ICDSC assessments, patient's ICDSC score was 3, close to the cut-off score of 4, indicating subsyndromal delirium. In two cases with ICD-10 delirium-positive assessment and both ICDSC and CAM-ICU false-negative assessments, patient behaviour was affected by expressive aphasia and severe pain. The sensitivity and specificity was 59% (95% CI 41-75) and 56% (95% CI 32-78), respectively for the CAM-ICU, and 85% (95% CI 70-94) and 75% (95% CI 51-92), respectively for the ICDSC (Table 3).

[**Fig. 2:** Intensive Care Delirium Screening Checklist (ICDSC) receiver operating characteristic (ROC) curve]

[**Appendix 1** Coordinates of the receiver operating characteristic (ROC) curve, sensitivity and specificity of the Intensive Care Delirium Screening Checklist (ICDSC)]

[**Table 2** CAM-ICU and ICDSC versus ICD-10]

[**Table 3** Criterion validation of the CAM-ICU and ICDSC,  $N=45$  /  $N=49$ ]

#### *Findings related to assessability and level of consciousness*

All patients with a normal level of consciousness (GCS 15) were considered assessable by psychiatrists. The lowest GCS associated with assessability for delirium was 10. Seven of seventeen (41%) patients with GCS 10 were assessable, while two of twenty (10%) patients with GCS 14 remained unassessable (Appendix 2). The level of consciousness fluctuated throughout the day in both UTA and assessable patients. At time of nurse assessment patients recorded as UTA vs assessable were RASS -1 (range, -2 to +2) vs 0 (range, -2 to +2) (Table 1). Fluctuations on the day of assessment were recorded on the observation chart. The lowest vs highest median RASS for

UTA patients was -3 (range -5 to -1) vs 0 (range -2 to +3). The lowest vs highest median RASS for assessable patients was -1 (range -4 to +2) vs 0 (range -2 to +3).

[**Table 1** Patient characteristics ( $N=74$ )]

[**Appendix 2** Patient assessability by GCS]

#### *Inter-rater reliability for the CAM-ICU and the ICDSC*

The IRR for the CAM-ICU demonstrated perfect agreement ( $\kappa = 1.0$ ) and the overall IRR for the ICDSC demonstrated an ICC value of 0.84 (95% CI 0.63-0.93).

## **DISCUSSION**

Our main findings are that both CAM-ICU and ICDSC could be clinically implemented in the Neuro-ICU. Nevertheless, psychiatrists using the ICD-10 considered a large proportion of patients successfully evaluated with the ICDSC/CAM-ICU as UTA, perhaps because of level of consciousness fluctuations. This is consistent with post-TBI neurorehabilitation patient clinical and delirium score evaluations, where DSM-based delirium symptoms, level of consciousness, memory impairment and agitation were frequent<sup>26</sup>. Bedside nurses may have had their assessments privileged by continuous observation over an entire shift, in contrast to a punctual psychiatric assessment in a neuro-cognitively changing patient. We conducted this study in a mixed Neuro-ICU population, which has, to our knowledge, not been done before. Comparing the assessable and non-assessable (UTA) groups, there was a difference in diagnosis with a higher proportion of patients with TBI in the UTA group. Also, more patients in the UTA group had lower GCS, and were mechanically ventilated and intubated at time of assessment. This suggests that the UTA group could be more severely damaged despite the similar APACHE II and SAPS II scores, explaining the difficulties in assessing these patients for delirium.

The CAM-ICU is used widely as a delirium screening tool in Danish and international ICUs. This instrument is easy to use, valid and reliable in the general ICU population; however, it provides a 'snapshot' of the mental state of the patient in question. We formally translated and validated the ICDSC in a Neuro-ICU for comparative purposes. The results were based on observations during 8-12 hour shifts, and exhibited a sensitivity and specificity resembling findings

in the general ICU population<sup>27</sup>. Screening with the CAM-ICU at night resulted in more missing data due to the inattention testing requirement, a feature highlighted as justifying the lower sensitivity (38%) than that found for the ICDSC (97%) in patients admitted to the ICU due to cardiac surgery<sup>28</sup>. Nevertheless, the performance documented with an AUROC of 0.77 in our study is lower than that reported in the original ICDSC general ICU validation study, where the AUROC was 0.90<sup>9</sup>. In our population, the CAM-ICU had less valid results in terms of sensitivity and specificity compared to other validation studies<sup>8,27,29</sup>. The study by Mitasova et al. (2012) showed that CAM-ICU performed better in patients with stroke in a Neuro-ICU, who had an initial median GCS of 14.5<sup>12</sup>. Conversely, CAM-ICU performance in patients with TBI in the Neuro-ICU with a median GCS of 14, was similar to our findings<sup>13</sup>.

Surprisingly, some patients assessed by psychiatrists with ICD-10 criteria and considered clinically delirious passed the CAM-ICU inattention testing. Regardless of the patient's delirium status, the ability to pass the CAM-ICU inattention test in patients with primary brain injury and severe brain dysfunction is intriguing from a pathophysiological point of view. Our decision of having RASS minus 2 as cut off for delirium assessment was based on the ICDSC work sheet as well as the CAM-ICU training manual, which describes RASS minus 3 as a grey area in some populations<sup>24</sup>. Our findings show that even a RASS of minus 2 can be challenging in this particular population.

The relatively high proportion of patients that were UTA in our study suggest that patients cannot always be labelled categorically as simply delirium positive or negative. This finding corresponds to a recent study addressing delirium screening by ICU nurses and physicians<sup>30</sup>. The discrepancy between the median GCS and RASS in the patients that were UTA, as presented in table 1, might be explained by the higher number of intubated patients among the UTA group. An intubated patient was given a verbal score of 'one' on the GCS since they are unable to speak, which limits the possibility to properly assess the GCS and can result in a lower score.

The gold standard in our study was delirium assessment according to ICD-10 performed by a psychiatrist. The psychiatrists based their evaluation on contextual information from clinical staff, hospital charts as well as their own bedside assessment of the patient, which wasn't concurrent with nurse's assessment. We assume this delay might explain inconsistencies in patients with a fluctuating level of consciousness. Furthermore, the ICD-10 diagnostic criteria for delirium differ slightly from the DSM-IV used in many previous validation studies<sup>8,9,12,13</sup>. The choice of ICD-10 was made because the DSM-IV was revised since the original CAM-ICU and ICDSC studies, and

because ICD-10 is the diagnostic standard in Europe. Validation and prevalence studies on delirium in general are likely to be affected by the well-described discrepancies associated with different diagnostic criteria and scales<sup>31</sup>; these methodological dimensions should be further investigated in future studies and considered in delirium-related publications.

### *Limitations*

Due to the unexpected high number of patients that were UTA we did not reach the required number of patients for final analysis. This reduces the robustness of our validation study and weakens the conclusion. Also, this study was conducted as a single centre study with no external validation. Larger studies in this challenging population are needed to verify our results.

### **Conclusions**

Two-thirds of patients with acute brain injury in the Neuro-ICU with a RASS of minus 2 or above were assessable for delirium. Delirium was found to be present in 67% (n=33) of assessable patients when tested by psychiatrists using the ICD-10 criteria as reference. The study suggests that the ICDSC is a valid tool to detect delirium in patients with acute brain injury in the Neuro-ICU, whereas the CAM-ICU is less valid. The potential inaccuracy of ICDSC, however, still warrants further exploring of delirium screening tools. Future studies are also recommended to investigate prevention, treatment, and long-term outcomes as well as exploring the patient experience.

### **References**

1. van den Boogaard M, Slooter AJC, Bruggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, Pretorius D, de Koning J, Simons KS, Dennesen PJW, Van der Voort PHJ, Houterman S, van der Hoeven JG, Pickkers P. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial. *Jama* 2018; 319: 680-90.
2. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose Nocturnal Dexmedetomidine Prevents ICU Delirium: A Randomized, Placebo-controlled Trial. *American journal of respiratory and critical care medicine* 2018.

3. Sharshar T, Citerio G, Andrews PJ, Chieriegato A, Latronico N, Menon DK, Puybasset L, Sandroni C, Stevens RD. Neurological examination of critically ill patients: a pragmatic approach. Report of an ESICM expert panel. *Intensive care medicine* 2014; 40: 484-95.
4. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, Hughes CG, Chandrasekhar R, Pun BT, Boehm LM, Elstad MR, Goodman RB, Bernard GR, Dittus RS, Ely EW. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *The Lancet Respiratory medicine* 2018; 6: 213-22.
5. Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. *American journal of respiratory and critical care medicine* 2014; 189: 658-65.
6. Maas MB, Naidech AM. Critical Care Neurology Perspective on Delirium. *Seminars in neurology* 2016; 36: 601-06.
7. Morandi A, Piva S, Ely EW, Myatra SN, Salluh JIF, Amare D, Azoulay E, Bellelli G, Csomos A, Fan E, Fagoni N, Girard TD, Heras La Calle G, Inoue S, Lim CM, Kaps R, Kotfis K, Koh Y, Misango D, Pandharipande PP, Permpikul C, Cheng Tan C, Wang DX, Sharshar T, Shehabi Y, Skrobik Y, Singh JM, Slooter A, Smith M, Tsuruta R, Latronico N. Worldwide Survey of the "Assessing Pain, Both Spontaneous Awakening and Breathing Trials, Choice of Drugs, Delirium Monitoring/Management, Early Exercise/Mobility, and Family Empowerment" (ABCDEF) Bundle. *Critical care medicine* 2017; 45: e1111-e22.
8. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *Jama* 2001; 286: 2703-10.
9. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive care medicine* 2001; 27: 859-64.
10. Ouimet S, Riker R, Bergeron N, Cossette M, Kavanagh B, Skrobik Y. Subsyndromal delirium in the ICU: evidence for a disease spectrum. *Intensive care medicine* 2007; 33: 1007-13.
11. Yu A, Teitelbaum J, Scott J, Gesin G, Russell B, Huynh T, Skrobik Y. Evaluating pain, sedation, and delirium in the neurologically critically ill-feasibility and reliability of standardized tools: a multi-institutional study. *Critical care medicine* 2013; 41: 2002-07.

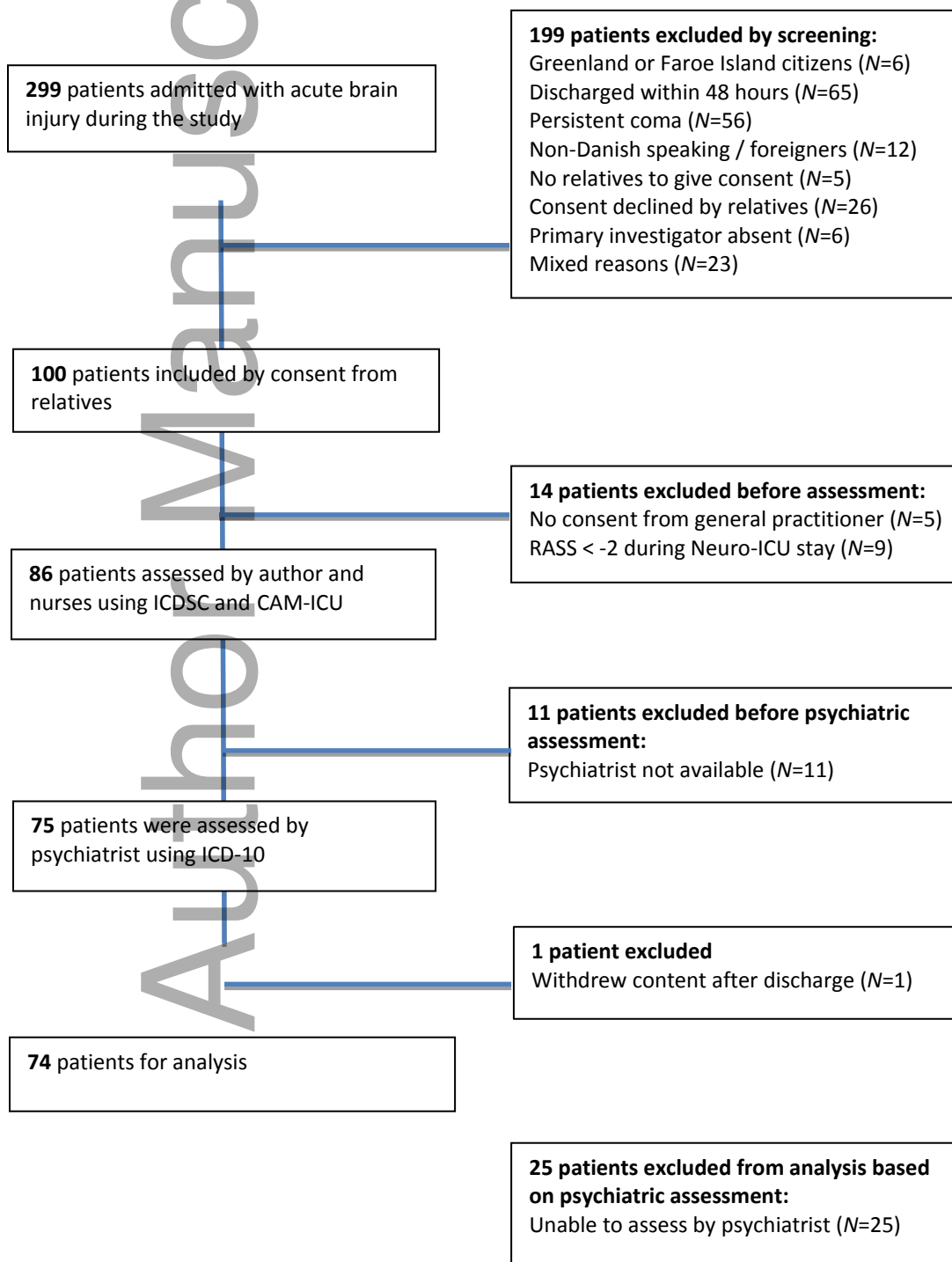
12. Mitasova A, Kostalova M, Bednarik J, Michalcakova R, Kasperek T, Balabanova P, Dusek L, Vohanka S, Ely EW. Poststroke delirium incidence and outcomes: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Critical care medicine* 2012; 40: 484-90.
13. Frenette AJ, Bebawi ER, Deslauriers LC, Tessier AA, Perreault MM, Delisle MS, Bertrand JC, Desjardins M, Rico P, Khwaja K, Burry LD, Bernard F, Williamson DR. Validation and comparison of CAM-ICU and ICDSC in mild and moderate traumatic brain injury patients. *Intensive care medicine* 2016; 42: 122-3.
14. Egerod I. Intensive care delirium: the new black. *Nurs Crit Care* 2013; 18: 164-65.
15. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013; 369: 1306-16.
16. Svenningsen H, Tonnesen EK, Videbech P, Frydenberg M, Christensen D, Egerod I. Intensive care delirium - effect on memories and health-related quality of life - a follow-up study. *J Clin Nurs* 2013.
17. Brummel NE, Jackson JC, Pandharipande PP, Thompson JL, Shintani AK, Dittus RS, Gill TM, Bernard GR, Ely EW, Girard TD. Delirium in the ICU and Subsequent Long-Term Disability Among Survivors of Mechanical Ventilation. *Critical care medicine* 2013.
18. Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, Truman B, Dittus R, Bernard R, Inouye SK. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive care medicine* 2001; 27: 1892-900.
19. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive care medicine* 2007; 33: 66-73.
20. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical care medicine* 2013; 41: 263-306.
21. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *American journal of respiratory and critical care medicine* 2002; 166: 1338-44.

22. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; 8: 94-104.
23. Neziraj M, Sarac KN, Samuelson K. The intensive care delirium screening checklist: translation and reliability testing in a Swedish ICU. *Acta Anaesthesiol Scand* 2011; 55: 819-26.
24. Ely E W (Translated into Danish by Svenningsen H LL, Christensen K, Egerod I). Confusion Assessment Method for the ICU (CAM-ICU). Training Manual. Danish version 2010.
25. Mansournia MA, Etminan M, Danaei G, Kaufman JS, Collins G. Handling time varying confounding in observational research. *BMJ (Clinical research ed)* 2017; 359: j4587.
26. Nakase-Thompson R, Sherer M, Yablon SA, Nick TG, Trzepacz PT. Acute confusion following traumatic brain injury. *Brain Inj* 2004; 18: 131-42.
27. Gusmao-Flores D, Salluh JI, Chalhoub RA, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Critical care (London, England)* 2012; 16: R115.
28. Nishimura K, Yokoyama K, Yamauchi N, Koizumi M, Harasawa N, Yasuda T, Mimura C, Igita H, Suzuki E, Uchiide Y, Seino Y, Nomura M, Yamazaki K, Ishigooka J. Sensitivity and specificity of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) for detecting post-cardiac surgery delirium: A single-center study in Japan. *Heart & lung : the journal of critical care* 2016; 45: 15-20.
29. Koga Y, Tsuruta R, Murata H, Matsuo K, Ito T, Ely EW, Shintani A, Wakamatsu H, Sanui M, Yamase H. Reliability and validity assessment of the Japanese version of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Intensive & critical care nursing* 2015; 31: 165-70.
30. Oxenboll-Collet M, Egerod I, Christensen V, Jensen J, Thomsen T. Nurses' and physicians' perceptions of Confusion Assessment Method for the intensive care unit for delirium detection: focus group study. *Nurs Crit Care* 2016.



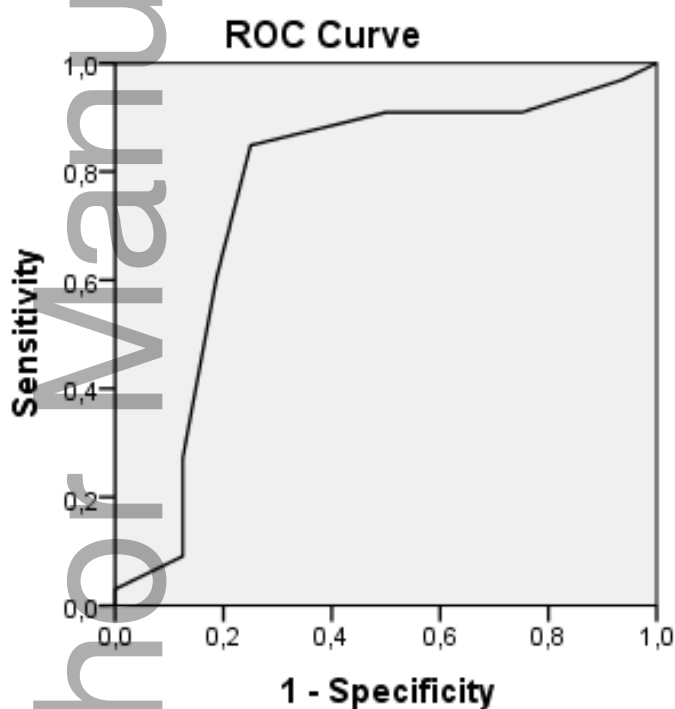
31. Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. Impact of different diagnostic criteria on prognosis of delirium: a prospective study. *Dementia and geriatric cognitive disorders* 2004; 18: 240-4.

**Fig. 1** Patient flow chart



49 patients assessable by ICD-10 and included in the final analysis

**Fig. 2** Intensive Care Delirium Screening Checklist (ICDSC) receiver operating characteristic (ROC) curve with an area under curve at 0.77(CI 95% 0.60 – 0.93);  $N=49$



Diagonal segments are produced by ties.

*Table 1*

Patient characteristics

Variable	All patients ( $N=74$ )	Assessable ( $N=49$ )	UTA ( $N=25$ )	<i>P value*</i>
Age, median (range) #	62 (19-88)	63 (19-82)	57 (19-88)	0.09
Females, n (%) α	38 (51 %)	27 (55%)	11(44 %)	0.37

Primary diagnosis, n (%) $\chi^2$				
Subarachnoid haemorrhage	36 (49%)	30 (61%)	6 (24%)	<0.05
Traumatic brain injury	20 (27%)	8 (16%)	12 (48%)	
Intracerebral haemorrhage and infarction	18 (24%)	11(22%)	7 (28%)	
APACHE II, median (range) #	22 (5-39)	22 (8-39)	22 (5-33)	0.65
SAPS II, media (range) #	36 (15-73)	32 (15-73)	42 (16-70)	0.07
GCS at admission, median (range) #	13 (3-15)	13 (3-15)	9 (3-14)	<0.05
GCS at assessment, median (range) #	13(10-15)	14 (10-15)	11 (10-14)	<0.001
RASS at assessment, median (range) #	-1 (-2/+2)	0 (-2 / +2)	-1 (-2 /+2)	<0.05
Mechanical ventilation and sedation during ICU stay, n (%) $\chi^2$	52 (70%)	30 (61%)	22 (88%)	<0.05
Agents used:				
Propofol	36 (49%)	22 (45%)	14 (56%)	
Propofol/midazolam	15 (20%)	7 (14%)	8 (32%)	
Propofol/midazolam/dexmedetomidine	1 (2%)	1 (2%)	-	
Sedation at assessment $\chi^2$	4 (5%)	1 <sup>a</sup> (2 %)	3 <sup>b</sup> (12 %)	0.11
Intubated at assessment $\chi^2$	14 (19%)	5 (10%)	9 (36%)	<0.05

APACHE = Acute Physiology and Chronic Health Evaluation, SAPS = Simplified Acute Physiology Score, GCS = Glasgow Coma Scale, RASS = Richmond Agitation Sedation Scale. UTA = unable to assess. \**P* values for the comparison between assessable and UTA patients, # = Mann-Whitney *U* test,  $\chi^2$  = Chi-square test, <sup>a</sup>Dexmedetomidine, <sup>b</sup>Propofol.

Table 2

CAM-ICU/ICDSC versus ICD-10

	ICD-10	Delirium positive	Delirium negative
CAM-ICU (N=45)			
Delirium positive		17 (True positive)	7 (False positive)
Delirium negative		12 (False negative)	9 (True negative)

ICDSC (N=49)			ICD
Delirium positive	28 (True positive)	4 (False positive)	-
Delirium negative	5 (False negative)	12 (True negative)	10=
			Inte

Cutoff score	Sensitivity %	Specificity %	International Classification of Diseases -10, CAM-ICU=Confusion Assessment Method for the ICU, ICDSC=Intensive Care Delirium Screening Checklist.
≥ 0	100%	0%	Note: Missing values in 4 cases in the CAM-ICU analysis.
≥ 1	97%	6%	
≥ 2	91%	25%	
≥ 3	91%	50%	
≥ 4	85%	75%	
≥ 5	61%	81%	

Table 3

Criterion validation of the CAM-ICU and ICDSC against ICD 10

	CAM-ICU (N=45)	ICDSC (N=49)
Sensitivity (95% CI)	59 % (95% CI 41 - 75)	85 % (95% CI 70 - 94)
Specificity (95% CI)	56 % (95% CI 32 - 78)	75 % (95% CI 51 - 92)
Positive predictive value (95% CI)	71 % (95% CI 51 - 86)	88 % (95% CI 73 - 96)
Negative predictive value (95% CI)	43 % (95% CI 23 - 67)	71 % (95% CI 47 - 88)
Overall accuracy (95% CI)	58 % (95% CI 43 - 72)	82 % (95% CI 71 - 93)

CAM-ICU=Confusion Assessment Method for the ICU, ICDSC=Intensive Care Delirium Screening Checklist.

Note: Missing values in 4 cases in the CAM-ICU analysis.

## Appendix 1

Coordinates of the receiver operating characteristic (ROC) curve, sensitivity and specificity of the Intensive Care Delirium Screening Checklist (ICDSC)

$\geq 6$	27%	88%	
$\geq 7$	9%	88%	
$\geq 8$	3%	100%	
<b>GCS</b>	<b>UTA</b>	<b>Assessable</b>	<b>by GCS</b>
	<b>(N=25)</b>	<b>(N=49)</b>	<b>(N=74)</b>
<b>10</b>	10 (40%)	7 (14%)	7/17 (41%)
<b>11</b>	6 (24%)	-	0/6 (0%)
<b>12</b>	6 (24%)	3 (6%)	3/9 (33%)
<b>13</b>	1 (4%)	14 (29%)	14/15 (93%)
<b>14</b>	2 (8%)	18 (37%)	18/20 (90%)
<b>15</b>	-	7 (14%)	7/7 (100 %)

Bold marks the best cut-off score

## Appendix 2 Patient assessability by GCS

GCS: Glasgow Coma Scale, UTA: Unable to assess. Values are numbers (%)

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